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(57) Abstract  Novel polynucleotides and the proteins encoded thereby are disclosed.			

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## SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

5           This application is a continuation-in-part of application Ser. No. 60/XXX,XXX (converted to a provisional application from non-provisional application Ser. No. 08/906,708), filed August 6, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

10           The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

15           Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein  
20 in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of  
25 DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

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### SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 864 to nucleotide 1340;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 1175;
- 10 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bi127\_5 deposited under accession number ATCC 98501;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bi127\_5 deposited under accession number ATCC 98501;
- 15 (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone bi127\_5 deposited under accession number ATCC 98501;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone bi127\_5 deposited under accession number ATCC 98501;
- 20 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:2;
- 25 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- 30 (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 864 to nucleotide 1340; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 1175; the nucleotide sequence of the full-length protein coding sequence of clone bi127\_5 deposited under accession number ATCC 98501; or the

nucleotide sequence of a mature protein coding sequence of clone bi127\_5 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone bi127\_5 deposited under accession number ATCC 98501. In yet other preferred  
5 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 104. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably  
10 twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:2, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 74 to amino acid 83 of SEQ ID NO:2.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ  
15 ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- 20 (b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 104;
- (c) fragments of the amino acid sequence of SEQ ID NO:2 comprising eight consecutive amino acids of SEQ ID NO:2; and
- (d) the amino acid sequence encoded by the cDNA insert of clone  
25 bi127\_5 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 104. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid  
30 sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:2, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 74 to amino acid 83 of SEQ ID NO:2.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- 5 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 46 to nucleotide 738;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 346 to nucleotide 738;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID  
10 NO:3 from nucleotide 688 to nucleotide 1425;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bl194\_2 deposited under accession number ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the  
15 cDNA insert of clone bl194\_2 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone bl194\_2 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA  
20 insert of clone bl194\_2 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment  
25 comprising eight consecutive amino acids of SEQ ID NO:4;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- 30 (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 46 to nucleotide 738; the nucleotide sequence of SEQ ID NO:3 from nucleotide 346 to nucleotide 738; the nucleotide sequence of SEQ ID NO:3 from

nucleotide 688 to nucleotide 1425; the nucleotide sequence of the full-length protein coding sequence of clone bl194\_2 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone bl194\_2 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone bl194\_2 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 171. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 110 to amino acid 119 of SEQ ID NO:4.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;
- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 171;
- (c) fragments of the amino acid sequence of SEQ ID NO:4 comprising eight consecutive amino acids of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone bl194\_2 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 171. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4

having biological activity, the fragment comprising the amino acid sequence from amino acid 110 to amino acid 119 of SEQ ID NO:4.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5                   (a)     a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b)     a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 234 to nucleotide 1235;
- (c)     a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 291 to nucleotide 1235;
- 10                  (d)     a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 209 to nucleotide 1050;
- (e)     a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cc130\_1 deposited under accession number ATCC 98501;
- 15                  (f)     a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501;
- (g)     a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone cc130\_1 deposited under accession number ATCC 98501;
- 20                  (h)     a polynucleotide encoding a mature protein encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501;
- (i)     a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- 25                  (j)     a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:6;
- (k)     a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- 30                  (l)     a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m)     a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).



Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 234 to nucleotide 1235; the nucleotide sequence of SEQ ID NO:5 from nucleotide 291 to nucleotide 1235; the nucleotide sequence of SEQ ID NO:5 from nucleotide 209 to nucleotide 1050; the nucleotide sequence of the full-length protein coding sequence of clone cc130\_1 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone cc130\_1 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 272. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:6, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 162 to amino acid 171 of SEQ ID NO:6.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 272;
- (c) fragments of the amino acid sequence of SEQ ID NO:6 comprising eight consecutive amino acids of SEQ ID NO:6; and
- (d) the amino acid sequence encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 272. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid

sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:6, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 162 to amino acid 171 of SEQ ID NO:6.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1554 to nucleotide 1784;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1659 to nucleotide 1784;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1508 to nucleotide 1865;
- 15 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ch582\_1 deposited under accession number ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501;
- 20 (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ch582\_1 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501;
- 25 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:8;
- 30 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 1554 to nucleotide 1784; the nucleotide sequence of SEQ ID NO:7 from nucleotide 1659 to nucleotide 1784; the nucleotide sequence of SEQ ID NO:7 from nucleotide 1508 to nucleotide 1865; the nucleotide sequence of the full-length protein coding sequence of clone ch582\_1 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone ch582\_1 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:8, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:8.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;
- (b) fragments of the amino acid sequence of SEQ ID NO:8 comprising eight consecutive amino acids of SEQ ID NO:8; and
- (c) the amino acid sequence encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:8, or a protein comprising a fragment of the amino acid sequence of

SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1375 to nucleotide 1605;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID  
10 NO:9 from nucleotide 1107 to nucleotide 1539;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cq294\_14 deposited under accession number ATCC 98501;
- (e) a polynucleotide encoding the full-length protein encoded by the  
15 cDNA insert of clone cq294\_14 deposited under accession number ATCC 98501;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone cq294\_14 deposited under accession number ATCC 98501;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA  
20 insert of clone cq294\_14 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment  
25 comprising eight consecutive amino acids of SEQ ID NO:10;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- 30 (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 1375 to nucleotide 1605; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1107 to nucleotide 1539; the nucleotide sequence of the full-length protein

coding sequence of clone cq294\_14 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone cq294\_14 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone cq294\_14 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 55. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:10, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:10.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 55;
- (c) fragments of the amino acid sequence of SEQ ID NO:10 comprising eight consecutive amino acids of SEQ ID NO:10; and
- (d) the amino acid sequence encoded by the cDNA insert of clone cq294\_14 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 55. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:10, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10

having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 66 to nucleotide 1880;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID  
10 NO:11 from nucleotide 1 to nucleotide 581;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone dd454\_1 deposited under accession number ATCC 98501;
- (e) a polynucleotide encoding the full-length protein encoded by the  
15 cDNA insert of clone dd454\_1 deposited under accession number ATCC 98501;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone dd454\_1 deposited under accession number ATCC 98501;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA  
20 insert of clone dd454\_1 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment  
25 comprising eight consecutive amino acids of SEQ ID NO:12;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- 30 (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 66 to nucleotide 1880; the nucleotide sequence of SEQ ID NO:11 from nucleotide 1 to nucleotide 581; the nucleotide sequence of the full-length protein

coding sequence of clone dd454\_1 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone dd454\_1 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone dd454\_1 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 172. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:12, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 297 to amino acid 306 of SEQ ID NO:12.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 172;
- (c) fragments of the amino acid sequence of SEQ ID NO:12 comprising eight consecutive amino acids of SEQ ID NO:12; and
- (d) the amino acid sequence encoded by the cDNA insert of clone dd454\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 172. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:12, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12

having biological activity, the fragment comprising the amino acid sequence from amino acid 297 to amino acid 306 of SEQ ID NO:12.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 462 to nucleotide 3170;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID  
10 NO:13 from nucleotide 1188 to nucleotide 1517;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone du157\_12 deposited under accession number ATCC 98724;
- (e) a polynucleotide encoding the full-length protein encoded by the  
15 cDNA insert of clone du157\_12 deposited under accession number ATCC 98724;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone du157\_12 deposited under accession number ATCC 98724;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA  
20 insert of clone du157\_12 deposited under accession number ATCC 98724;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment  
25 comprising eight consecutive amino acids of SEQ ID NO:14;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- 30 (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 462 to nucleotide 3170; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1188 to nucleotide 1517; the nucleotide sequence of the full-length protein



coding sequence of clone du157\_12 deposited under accession number ATCC 98724; or the nucleotide sequence of a mature protein coding sequence of clone du157\_12 deposited under accession number ATCC 98724. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone du157\_12 deposited under accession number ATCC 98724. In yet other preferred  
5       embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 251 to amino acid 352. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14  
10       having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:14, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 446 to amino acid 455 of SEQ ID NO:14.

15       Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- 20               (a)     the amino acid sequence of SEQ ID NO:14;
- (b)     the amino acid sequence of SEQ ID NO:14 from amino acid 251 to amino acid 352;
- (c)     fragments of the amino acid sequence of SEQ ID NO:14 comprising eight consecutive amino acids of SEQ ID NO:14; and
- 25               (d)     the amino acid sequence encoded by the cDNA insert of clone du157\_12 deposited under accession number ATCC 98724;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14 or the amino acid sequence of SEQ ID NO:14 from amino acid 251 to amino acid 352. In further preferred  
30       embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:14, or a protein comprising a fragment of the amino acid sequence of

SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 446 to amino acid 455 of SEQ ID NO:14.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 865 to nucleotide 1158;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID  
10 NO:15 from nucleotide 1108 to nucleotide 1158;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 764;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone du372\_1 deposited under accession  
15 number ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone du372\_1 deposited under accession number  
20 ATCC 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- 25 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:16;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- 30 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 865 to nucleotide 1158; the nucleotide sequence of SEQ ID NO:15 from nucleotide 1108 to nucleotide 1158; the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 764; the nucleotide sequence of the full-length protein coding sequence of clone du372\_1 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone du372\_1 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 69 to amino acid 98. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:16, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 44 to amino acid 53 of SEQ ID NO:16.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) the amino acid sequence of SEQ ID NO:16 from amino acid 69 to amino acid 98;
- (c) fragments of the amino acid sequence of SEQ ID NO:16 comprising eight consecutive amino acids of SEQ ID NO:16; and
- (d) the amino acid sequence encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 69 to amino acid 98. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid

sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:16, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 44 to amino acid 53 of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 32 to nucleotide 586;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 92 to nucleotide 586;
- 15 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 481;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ej90\_5 deposited under accession number ATCC 98501;
- 20 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ej90\_5 deposited under accession number ATCC 98501;
- 25 (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;
- 30 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:18;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 32 to nucleotide 586; the nucleotide sequence of SEQ ID NO:17 from nucleotide 92 to nucleotide 586; the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 481; the nucleotide sequence of the full-length protein coding sequence of clone ej90\_5 deposited under accession number ATCC 98501; or the nucleotide sequence of a mature protein coding sequence of clone ej90\_5 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 150. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:18, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 87 to amino acid 96 of SEQ ID NO:18.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:18;
- (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 150;
- (c) fragments of the amino acid sequence of SEQ ID NO:18 comprising eight consecutive amino acids of SEQ ID NO:18; and
- (d) the amino acid sequence encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence

of SEQ ID NO:18 from amino acid 1 to amino acid 150. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID  
5 NO:18, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 87 to amino acid 96 of SEQ ID NO:18.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 10 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 281 to nucleotide 1786;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID  
15 NO:19 from nucleotide 332 to nucleotide 1786;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 1 to nucleotide 574;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ic2\_6 deposited under accession number  
20 ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ic2\_6 deposited under accession number ATCC  
25 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;
- 30 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:20;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 281 to nucleotide 1786; the nucleotide sequence of SEQ ID NO:19 from nucleotide 332 to nucleotide 1786; the nucleotide sequence of SEQ ID NO:19 from nucleotide 1 to nucleotide 574; the nucleotide sequence of the full-length protein coding sequence of clone ic2\_6 deposited under accession number ATCC 98501; or the nucleotide  
10 sequence of a mature protein coding sequence of clone ic2\_6 deposited under accession number ATCC 98501. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid  
15 sequence of SEQ ID NO:20 from amino acid 1 to amino acid 98. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:20, or a polynucleotide encoding  
20 a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 246 to amino acid 255 of SEQ ID NO:20.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:20;
- (b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to  
30 amino acid 98;
- (c) fragments of the amino acid sequence of SEQ ID NO:20 comprising eight consecutive amino acids of SEQ ID NO:20; and
- (d) the amino acid sequence encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 98. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:20, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 246 to amino acid 255 of SEQ ID NO:20.

10 In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

20 The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

25 Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

### 30 BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.



DETAILED DESCRIPTIONISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide  
5 sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature forms) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by  
10 expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal  
15 sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

20 Clone "bi127\_5"

A polynucleotide of the present invention has been identified as clone "bi127\_5". bi127\_5 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was  
25 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bi127\_5 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bi127\_5 protein").

The nucleotide sequence of bi127\_5 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted  
30 amino acid sequence of the bi127\_5 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bi127\_5 should be approximately 2500 bp.

The nucleotide sequence disclosed herein for bi127\_5 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bi127\_5 demonstrated at least some similarity with sequences identified as AA055840 (zf20c06.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 377482 3'), AA334304 (EST38496 Embryo, 9 week Homo sapiens cDNA 5' end similar to similar to H. sapiens hypothetical protein, chromosome 3p21.1 gene sequence (GB:L13435)), AA399397 (zt59f11.r1 Soares testis NHT Homo sapiens cDNA clone 726669 5'), AA576692 (nm73a07.s1 NCI\_CGAP\_Co9 Homo sapiens cDNA clone IMAGE:1073844), H01918 (yj29a07.s1 Homo sapiens cDNA clone 150132 3'), H94897 (yu57h08.s1 Homo sapiens cDNA clone 230271 3'), L13435 (Human chromosome 3p21.1 gene sequence), R85965 (yt66g02.s1 Soares retina N2b4HR Homo sapiens cDNA clone 275499 3'), and X95828 (H.sapiens DNA NotI jumping clone J32A032D). Based upon sequence similarity, bi127\_5 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the bi127\_5 protein sequence centered around amino acid 15 of SEQ ID NO:2.

#### Clone "bl194\_2"

A polynucleotide of the present invention has been identified as clone "bl194\_2". bl194\_2 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bl194\_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bl194\_2 protein").

The nucleotide sequence of bl194\_2 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bl194\_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 88 to 100 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 101, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bl194\_2 should be approximately 1600 bp.

The nucleotide sequence disclosed herein for bl194\_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bl194\_2 demonstrated at least some similarity with sequences identified as AA136931 (zn97f05.s1 Stratagene fetal retina 937202 Homo sapiens cDNA clone 566145 3'), AA148976 (zn99e10.r1 Stratagene colon (#937204) Homo sapiens cDNA clone 566346 5'), AA148977 (zn99e10.s1 Stratagene colon (#937204) Homo sapiens cDNA clone 566346 3'), AA196293 (zp92g07.s1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 627708 3'), AA487754 (ab13e12.r1 Stratagene lung (#937210) Homo sapiens cDNA clone 840718 5'), H01254 (yj27b02.r1 Homo sapiens cDNA clone 149931 5'), H86324 (yt05f07.r1 Homo sapiens cDNA clone 223429 5'), N23958 (yx71c02.s1 Homo sapiens cDNA clone 267170 3'), N31859 (yx71c02.r1 Homo sapiens cDNA clone 267170 5'), R01674 (ye76b07.s1 Homo sapiens cDNA clone 123637 3'), and T78480 (yd68g08.s1 Homo sapiens cDNA clone 113438 3'). The predicted amino acid sequence disclosed herein for bl194\_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted bl194\_2 protein demonstrated at least some similarity to the sequence identified as S75895 (NADH dehydrogenase subunit 2, ND2 [human, brain, Peptide Mitochondrial Partial Mutant, 79 aa] [Homo sapiens]). Based upon sequence similarity, bl194\_2 proteins and each similar protein or peptide may share at least some activity.

#### Clone "cc130\_1"

A polynucleotide of the present invention has been identified as clone "cc130\_1". cc130\_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cc130\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cc130\_1 protein").

The nucleotide sequence of cc130\_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the cc130\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 7 to 19 are a predicted leader/signal

sequence, with the predicted mature amino acid sequence beginning at amino acid 20, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cc130\_1 should be approximately 2500 bp.

5       The nucleotide sequence disclosed herein for cc130\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cc130\_1 demonstrated at least some similarity with sequences identified as T21181 (Human gene signature HUMGS02491), T70127 (yc17d06.r1 Homo sapiens cDNA clone 80939 5' similar to SP:BUTY\_BOVIN P18892 BUTYROPHILIN  
10 PRECURSOR), T92875 (ye27h03.r1 Homo sapiens cDNA clone 118997 5'), U39576 (Human butyrophilin precursor mRNA, complete cds), U90546 (Human butyrophilin (BTF4) mRNA, complete cds), and W69453 (zd45e02.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 343610 3'). The predicted amino acid sequence disclosed herein for cc130\_1 was searched against the GenPept and GeneSeq amino acid sequence  
15 databases using the BLASTX search protocol. The predicted cc130\_1 protein demonstrated at least some similarity to sequences identified as M35551 (BOVBUTBT1\_1 Bovine butyrophilin mRNA, complete cds. [Bos taurus]), R71361 (Human truncated MOG), U39576 (butyrophilin precursor [Homo sapiens]), and U90546 (butyrophilin [Homo sapiens]). Butyrophilin may function in the secretion of milk-fat  
20 droplets and may act as a specific membrane-associated receptor for the association of cytoplasmic droplets with the apical plasma membrane. The subcellular location of butyrophilin is that of a Type I membrane protein. Butyrophilin also exhibits tissue specificity, being expressed in mammary tissue and secreted in association with the milk-fat-globule membrane during lactation. Butyrophilin is also homologous to MOG  
25 (myelinoligo dendrocyte protein) which is used to treat auto-immune diseases. Both butyrophilin and MOG are homologous in the same amino acids to an immunoglobulin variable region; this may indicate the existence of a protein-protein binding (receptor) site. Based upon sequence similarity, cc130\_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts an additional  
30 potential transmembrane domain within the cc130\_1 protein sequence centered around amino acid 255 of SEQ ID NO:6.

Clone "ch582\_1"

A polynucleotide of the present invention has been identified as clone "ch582\_1". ch582\_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was  
5 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ch582\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ch582\_1 protein").

The nucleotide sequence of ch582\_1 as presently determined is reported in SEQ  
10 ID NO:7. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ch582\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8. Amino acids 23 to 35 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 36, or are a transmembrane domain.

15 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ch582\_1 should be approximately 2300 bp.

The nucleotide sequence of ch582\_1 indicates that it may contain one or more repetitive elements.

20 Clone "cq294\_14"

A polynucleotide of the present invention has been identified as clone "cq294\_14". cq294\_14 was isolated from a human adult heart cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was  
25 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cq294\_14 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cq294\_14 protein").

The nucleotide sequence of cq294\_14 as presently determined is reported in SEQ  
ID NO:9. What applicants presently believe to be the proper reading frame and the  
30 predicted amino acid sequence of the cq294\_14 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cq294\_14 should be approximately 1850 bp.

The nucleotide sequence disclosed herein for cq294\_14 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cq294\_14 demonstrated at least some similarity with sequences identified as AA133962 (zl34c12.s1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 503830 3'), AA447968 (zv83h10.s1 Soares total fetus Nb2HF8 9w Homo sapiens cDNA clone 760291 3'), N47086 (yy85c08.s1 Homo sapiens cDNA clone 280334 3'), R33663 (yh82g06.s1 Homo sapiens cDNA clone 136282 3'), R45544 (yg43g12.s1 Homo sapiens cDNA clone 35358 3'), R77637 (yi76h09.s1 Homo sapiens cDNA clone 145217 3'), and W37736 (zc10h10.r1 Soares parathyroid tumor NbHPA Homo sapiens cDNA clone). Based upon sequence similarity, cq294\_14 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts three potential transmembrane domains within the cq294\_14 protein sequence, centered around amino acids 15, 25, and 50 of SEQ ID NO:10, respectively. The nucleotide sequence of cq294\_14 indicates that it may contain one or more repetitive elements.

#### Clone "dd454\_1"

A polynucleotide of the present invention has been identified as clone "dd454\_1". dd454\_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. dd454\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "dd454\_1 protein").

The nucleotide sequence of dd454\_1 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the dd454\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone dd454\_1 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for dd454\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. dd454\_1 demonstrated at least some similarity with sequences identified as AA393499 (zt73g06.r1 Soares testis NHT Homo sapiens cDNA clone 728026

5') and AA430063 (zw67a12.s1 Soares testis NHT Homo sapiens cDNA clone 781246 3'). Based upon sequence similarity, dd454\_1 proteins and each similar protein or peptide may share at least some activity.

5        Clone "du157\_12"

A polynucleotide of the present invention has been identified as clone "du157\_12". du157\_12 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer  
10 analysis of the amino acid sequence of the encoded protein. du157\_12 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "du157\_12 protein").

The nucleotide sequence of du157\_12 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the  
15 predicted amino acid sequence of the du157\_12 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone du157\_12 should be approximately 4050 bp.

The nucleotide sequence disclosed herein for du157\_12 was searched against the  
20 GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. du157\_12 demonstrated at least some similarity with sequences identified as AA164862 (zq41g04.r1 Stratagene hNT neuron (#937233) Homo sapiens cDNA clone 632310 5'), AA284379 (zs59a07.r1 NCI\_CGAP\_GCB1 Homo sapiens cDNA clone IMAGE:701748 5'), and T22493 (Human gene signature HUMGS04104). Based  
25 upon sequence similarity, du157\_12 proteins and each similar protein or peptide may share at least some activity.

Clone "du372\_1"

A polynucleotide of the present invention has been identified as clone "du372\_1".  
30 du372\_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. du372\_1 is a full-length clone,

including the entire coding sequence of a secreted protein (also referred to herein as "du372\_1 protein").

The nucleotide sequence of du372\_1 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the du372\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 69 to 81 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 82, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone du372\_1 should be approximately 1500 bp.

The nucleotide sequence disclosed herein for du372\_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. du372\_1 demonstrated at least some similarity with sequences identified as AA099051 (zn45c07.r1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 550380 5'), AA424986 (zw06g01.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 768528 5'), AA480114 (zv41h05.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 756249 3'), H73153 (yu26e11.r1 Homo sapiens cDNA clone 234956 5'), and H73629 (yu26f11.r1 Homo sapiens cDNA clone 234957 5'). Based upon sequence similarity, du372\_1 proteins and each similar protein or peptide may share at least some activity.

#### Clone "ej90\_5"

A polynucleotide of the present invention has been identified as clone "ej90\_5". ej90\_5 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ej90\_5 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ej90\_5 protein").

The nucleotide sequence of ej90\_5 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ej90\_5 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 8 to 20 are a predicted



leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 21, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ej90\_5 should be approximately 850 bp.

5       The nucleotide sequence disclosed herein for ej90\_5 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ej90\_5 demonstrated at least some similarity with sequences identified as AA099387 (zk85e10.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 489642 5'), AA099388 (zk85e10.s1 Soares pregnant uterus NbHPU Homo sapiens  
10 cDNA clone 489642 3'), AA256657 (zr85c06.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 682474 5'), and X85111 (X.laevis mRNA for XEL-1). Based upon sequence similarity, ej90\_5 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts an additional potential transmembrane domain within the ej90\_5 protein sequence centered around amino acid 164  
15 of SEQ ID NO:18.

#### Clone "ic2\_6"

A polynucleotide of the present invention has been identified as clone "ic2\_6". ic2\_6 was isolated from a human adult retina (retinoblastoma WERI-Rb1) cDNA library  
20 using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ic2\_6 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ic2\_6 protein").

25       The nucleotide sequence of ic2\_6 as presently determined is reported in SEQ ID NO:19. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ic2\_6 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 5 to 17 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at  
30 amino acid 18, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ic2\_6 should be approximately 2000 bp.

The nucleotide sequence disclosed herein for ic2\_6 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ic2\_6 demonstrated at least some similarity with sequences identified as AA104139 (mp03a12.r1 Stratagene mouse heart (#937316) *Mus musculus* cDNA clone 568126 5'), N39195 (yv26e08.s1 *Homo sapiens* cDNA clone 243878 3'), and Z59762 (*H.sapiens* CpG DNA, clone 171h5, reverse read cpg171h5.rt1a). Based upon sequence similarity, ic2\_6 proteins and each similar protein or peptide may share at least some activity.

10        Deposit of Clones

Clones bi127\_5, bl194\_2, cc130\_1, ch582\_1, cq294\_14, dd454\_1, du157\_9, du372\_1, ej90\_5, and ic2\_6 were deposited on August 5, 1997 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and were given the accession number ATCC 15 98501, from which each clone comprising a particular polynucleotide is obtainable. Clone du157\_12 is an additional isolate of clone du157\_9 and was deposited on April 7, 1998 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and was given the accession number ATCC 98724, from which the du157\_12 clone comprising a 20 particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b), and the term of the deposit will comply with 37 C.F.R. § 1.806.

Each clone has been transfected into separate bacterial cells (*E. coli*) in this 25 composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Figures 1A and 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate 30 cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped"

(i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the  
 5 vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences  
 10 provided herein, or from a combination of those sequences. The sequence of an oligonucleotide probe that was used to isolate or to sequence each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

	<u>Clone</u>	<u>Probe Sequence</u>
15	bi127_5	SEQ ID NO:21
	bl194_2	SEQ ID NO:22
	cc130_1	SEQ ID NO:23
	ch582_1	SEQ ID NO:24
	cq294_14	SEQ ID NO:25
20	dd454_1	SEQ ID NO:26
	du157_12	SEQ ID NO:27
	du372_1	SEQ ID NO:28
	ej90_5	SEQ ID NO:29
	ic2_6	SEQ ID NO:30

25

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).  
 30

The design of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

- (b) It should be designed to have a  $T_m$  of approx. 80 °C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with  $\gamma$ - $^{32}\text{P}$  ATP (specific activity 6000 Ci/mmol) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately  $4 \times 10^6$  dpm/pmol.

- 10 The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu\text{l}$  of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100  $\mu\text{g}/\text{ml}$ . The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100  $\mu\text{g}/\text{ml}$  and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

- 15 Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

- 20 The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100  $\mu\text{g}/\text{ml}$  of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to  $1 \times 10^6$  dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.
- 25
- 30

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, *Bio/Technology* 10, 773-778 (1992) and in R.S. McDowell, *et al.*, *J. Amer. Chem. Soc.* 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that

has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The  
5 desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have  
10 multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are  
15 also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation  
20 can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988,  
25 *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of  
30 assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that

the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with  
5 amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and  
10 identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

15 Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence  
20 identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when  
25 aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated from mammalian species. Most preferably, species homologues are those isolated from certain mammalian  
30 species such as, for example, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadryas*, *Cercopithecus aethiops*, *Cebus capucinus*, *Aotus trivirgatus*, *Sanguinus oedipus*, *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Oryctolagus cuniculus*, *Bos taurus*,

*Ovis aries*, *Sus scrofa*, and *Equus caballus*, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuñez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature* 5 *Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682-690; Lyons *et al.*, 1997, *Nature* *Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.



	Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) <sup>‡</sup>	Hybridization Temperature and Buffer <sup>†</sup>	Wash Temperature and Buffer <sup>†</sup>
5	A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
	B	DNA:DNA	<50	T <sub>B</sub> <sup>*</sup> ; 1xSSC	T <sub>B</sub> <sup>*</sup> ; 1xSSC
	C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
	D	DNA:RNA	<50	T <sub>D</sub> <sup>*</sup> ; 1xSSC	T <sub>D</sub> <sup>*</sup> ; 1xSSC
	E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
	F	RNA:RNA	<50	T <sub>F</sub> <sup>*</sup> ; 1xSSC	T <sub>F</sub> <sup>*</sup> ; 1xSSC
10	G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
	H	DNA:DNA	<50	T <sub>H</sub> <sup>*</sup> ; 4xSSC	T <sub>H</sub> <sup>*</sup> ; 4xSSC
	I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
	J	DNA:RNA	<50	T <sub>J</sub> <sup>*</sup> ; 4xSSC	T <sub>J</sub> <sup>*</sup> ; 4xSSC
	K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
	L	RNA:RNA	<50	T <sub>L</sub> <sup>*</sup> ; 2xSSC	T <sub>L</sub> <sup>*</sup> ; 2xSSC
15	M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
	N	DNA:DNA	<50	T <sub>N</sub> <sup>*</sup> ; 6xSSC	T <sub>N</sub> <sup>*</sup> ; 6xSSC
	O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
	P	DNA:RNA	<50	T <sub>P</sub> <sup>*</sup> ; 6xSSC	T <sub>P</sub> <sup>*</sup> ; 6xSSC
	Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
20	R	RNA:RNA	<50	T <sub>R</sub> <sup>*</sup> ; 4xSSC	T <sub>R</sub> <sup>*</sup> ; 4xSSC

<sup>‡</sup>: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

<sup>†</sup>: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

<sup>\*</sup>T<sub>B</sub> - T<sub>R</sub>: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T<sub>m</sub>) of the hybrid, where T<sub>m</sub> is determined according to the following equations. For hybrids less than 18 base pairs in length, T<sub>m</sub>(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T<sub>m</sub>(°C) = 81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant

methy1 or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance  
5 with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

10 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,  
15 including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally  
20 provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another  
25 amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be  
30 expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

## USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

### Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, those described in Gyuris *et al.*, 1993, *Cell* 75: 791-803 and in Rossi *et al.*, 1997, *Proc. Natl. Acad. Sci. USA* 94: 8405-8410, all of which are incorporated by reference herein) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially  
5 binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

10 Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook,  
15 J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

#### Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as  
20 nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or  
25 capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

#### Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either  
30 inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is

evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured  
5 by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter  
10 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node  
15 cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon  $\gamma$ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

20 Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature*  
25 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991;  
30 Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for



example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient  
5 by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic  
10 acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function  
15 (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides.  
20 For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used  
25 to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II  
30 molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I  $\alpha$  chain protein and  $\beta_2$  microglobulin protein or an MHC class II  $\alpha$  chain protein and an MHC class II  $\beta$  chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnoli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

#### Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of

5 hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or

10 *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

15 Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. *Cellular Biology* 15:141-151, 1995; Keller et

20 al., *Molecular and Cellular Biology* 13:473-486, 1993; McClanahan et al., *Blood* 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of*

25 *Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., *Experimental Hematology* 22:353-359,

30 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

#### Tissue Growth Activity

5           A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

          A protein of the present invention, which induces cartilage and/or bone growth  
10   in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of  
15   congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

          A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce  
20   differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

25           Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and  
30   other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce  
5 differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in  
10 the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve  
15 tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present  
20 invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of  
25 non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac)  
30 and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.



A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting  
5 differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described  
10 in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium ).

Assays for wound healing activity include, without limitation, those described in:  
Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year  
15 Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related  
20 activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$  family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts  
25 of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example,  
30 United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

5

#### Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells.

- 10 Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses
- 15 against the tumor or infecting agent.

- A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population
- 20 of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

- Assays for chemotactic activity (which will identify proteins that induce or prevent
- 25 chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene
- 30 Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. *J. Clin. Invest.* 95:1370-1376, 1995; Lind et al. *APMIS* 103:140-146, 1995; Muller et al. *Eur. J. Immunol.* 25: 1744-1748; Gruber et al. *J. of Immunol.* 152:5860-5867, 1994; Johnston et al. *J. of Immunol.* 153: 1762-1768, 1994.

#### Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

10       The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 15 35:467-474, 1988.

#### Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

30       The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and

Wiley-Interscience- (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenberg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 5 1995.

#### Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in 10 the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat 15 inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting 20 from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

#### Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major 25 roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

30 The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

5 E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to  
10 their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention  
15 encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue  
20 in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and  
25 polynucleotides of the present invention encoding such proteins, can be used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the  
30 cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides  
5 encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

#### 10 Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or  
15 tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

#### 20 Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height,  
25 weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein,  
30 carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen  
5 in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### **ADMINISTRATION AND DOSING**

A protein of the present invention (from whatever source derived, including  
10 without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the  
15 effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem  
20 cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included  
25 in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers  
30 or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein

and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines



or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If  
5 administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical  
10 composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is  
15 administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention.  
20 When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid  
25 form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present  
30 invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium

Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

5           The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician  
10 will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100  
15 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

          The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is  
20 contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

          Protein of the invention may also be used to immunize animals to obtain  
25 polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in  
30 R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where

abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

5 For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably  
10 be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the  
15 methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical  
20 applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium  
25 sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other  
30 ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions  
5 from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of  
10 carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to  
15 provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in  
20 question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- $\alpha$  and TGF- $\beta$ ), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to  
25 humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of  
30 a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect

the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

5 Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

10 Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide selected from the group consisting of:
  - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 864 to nucleotide 1340;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 1175;
  - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bi127\_5 deposited under accession number ATCC 98501;
  - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bi127\_5 deposited under accession number ATCC 98501;
  - (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone bi127\_5 deposited under accession number ATCC 98501;
  - (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone bi127\_5 deposited under accession number ATCC 98501;
  - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
  - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:2;
  - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
  - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
  - (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).
2. The polynucleotide of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.
3. A host cell transformed with the polynucleotide of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein encoded by the polynucleotide of claim 2, which process comprises:
  - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
  - (b) purifying said protein from the culture.
6. A protein produced according to the process of claim 5.
7. A protein comprising an amino acid sequence selected from the group consisting of:
  - (a) the amino acid sequence of SEQ ID NO:2;
  - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 104;
  - (c) fragments of the amino acid sequence of SEQ ID NO:2 comprising eight consecutive amino acids of SEQ ID NO:2; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone bi127\_5 deposited under accession number ATCC 98501;the protein being substantially free from other mammalian proteins.
8. The protein of claim 7, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
9. The protein of claim 7, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 104.
10. A composition comprising the protein of claim 7 and a pharmaceutically acceptable carrier.
11. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.
12. An isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 46 to nucleotide 738;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 346 to nucleotide 738;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 688 to nucleotide 1425;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone b1194\_2 deposited under accession number ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone b1194\_2 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone b1194\_2 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone b1194\_2 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:4;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

13. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;



- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 171;
  - (c) fragments of the amino acid sequence of SEQ ID NO:4 comprising eight consecutive amino acids of SEQ ID NO:4; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone bl194\_2 deposited under accession number ATCC 98501;
- the protein being substantially free from other mammalian proteins.

14. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.
15. An isolated polynucleotide selected from the group consisting of:
  - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 234 to nucleotide 1235;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 291 to nucleotide 1235;
  - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 209 to nucleotide 1050;
  - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cc130\_1 deposited under accession number ATCC 98501;
  - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501;
  - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone cc130\_1 deposited under accession number ATCC 98501;
  - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501;
  - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
  - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:6;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

16. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 272;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising eight consecutive amino acids of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone cc130\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins.

17. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

18. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1554 to nucleotide 1784;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1659 to nucleotide 1784;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1508 to nucleotide 1865;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ch582\_1 deposited under accession number ATCC 98501;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501;

(g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ch582\_1 deposited under accession number ATCC 98501;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:8;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

19. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8 comprising eight consecutive amino acids of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone ch582\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins.

20. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

21. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1375 to nucleotide 1605;

- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1107 to nucleotide 1539;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cq294\_14 deposited under accession number ATCC 98501;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cq294\_14 deposited under accession number ATCC 98501;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone cq294\_14 deposited under accession number ATCC 98501;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone cq294\_14 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:10;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

22. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 55;
- (c) fragments of the amino acid sequence of SEQ ID NO:10 comprising eight consecutive amino acids of SEQ ID NO:10; and
- (d) the amino acid sequence encoded by the cDNA insert of clone cq294\_14 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins.

23. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.
24. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 66 to nucleotide 1880;
  - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 1 to nucleotide 581;
  - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone dd454\_1 deposited under accession number ATCC 98501;
  - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone dd454\_1 deposited under accession number ATCC 98501;
  - (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone dd454\_1 deposited under accession number ATCC 98501;
  - (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone dd454\_1 deposited under accession number ATCC 98501;
  - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
  - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:12;
  - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
  - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
  - (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).
25. A protein comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:12;

- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 172;
  - (c) fragments of the amino acid sequence of SEQ ID NO:12 comprising eight consecutive amino acids of SEQ ID NO:12; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone dd454\_1 deposited under accession number ATCC 98501;
- the protein being substantially free from other mammalian proteins.

26. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

27. An isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 462 to nucleotide 3170;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1188 to nucleotide 1517;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone du157\_12 deposited under accession number ATCC 98724;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone du157\_12 deposited under accession number ATCC 98724;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone du157\_12 deposited under accession number ATCC 98724;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone du157\_12 deposited under accession number ATCC 98724;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:14;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

28. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 251 to amino acid 352;

(c) fragments of the amino acid sequence of SEQ ID NO:14 comprising eight consecutive amino acids of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone du157\_12 deposited under accession number ATCC 98724;

the protein being substantially free from other mammalian proteins.

29. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

30. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 865 to nucleotide 1158;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1108 to nucleotide 1158;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 764;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone du372\_1 deposited under accession number ATCC 98501;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501;

(g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone du372\_1 deposited under accession number ATCC 98501;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:16;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

31. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 69 to amino acid 98;

(c) fragments of the amino acid sequence of SEQ ID NO:16 comprising eight consecutive amino acids of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone du372\_1 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins.

32. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

33. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;



- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 32 to nucleotide 586;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 92 to nucleotide 586;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 481;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ej90\_5 deposited under accession number ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ej90\_5 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:18;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

34. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:18;
- (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 150;

- (c) fragments of the amino acid sequence of SEQ ID NO:18 comprising eight consecutive amino acids of SEQ ID NO:18; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone ej90\_5 deposited under accession number ATCC 98501;
- the protein being substantially free from other mammalian proteins.

35. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.

36. An isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 281 to nucleotide 1786;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 332 to nucleotide 1786;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 1 to nucleotide 574;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ic2\_6 deposited under accession number ATCC 98501;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ic2\_6 deposited under accession number ATCC 98501;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:20;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

37. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:20;
- (b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 98;
- (c) fragments of the amino acid sequence of SEQ ID NO:20 comprising eight consecutive amino acids of SEQ ID NO:20; and
- (d) the amino acid sequence encoded by the cDNA insert of clone ic2\_6 deposited under accession number ATCC 98501;

the protein being substantially free from other mammalian proteins.

38. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:19.

FIGURE 1A

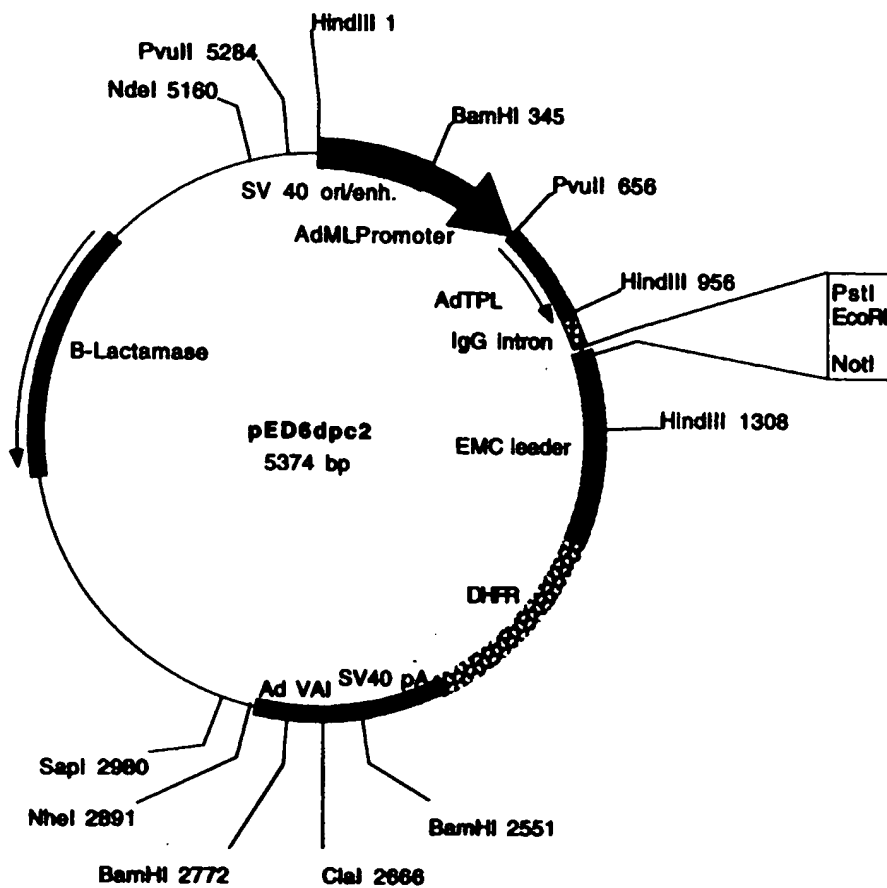
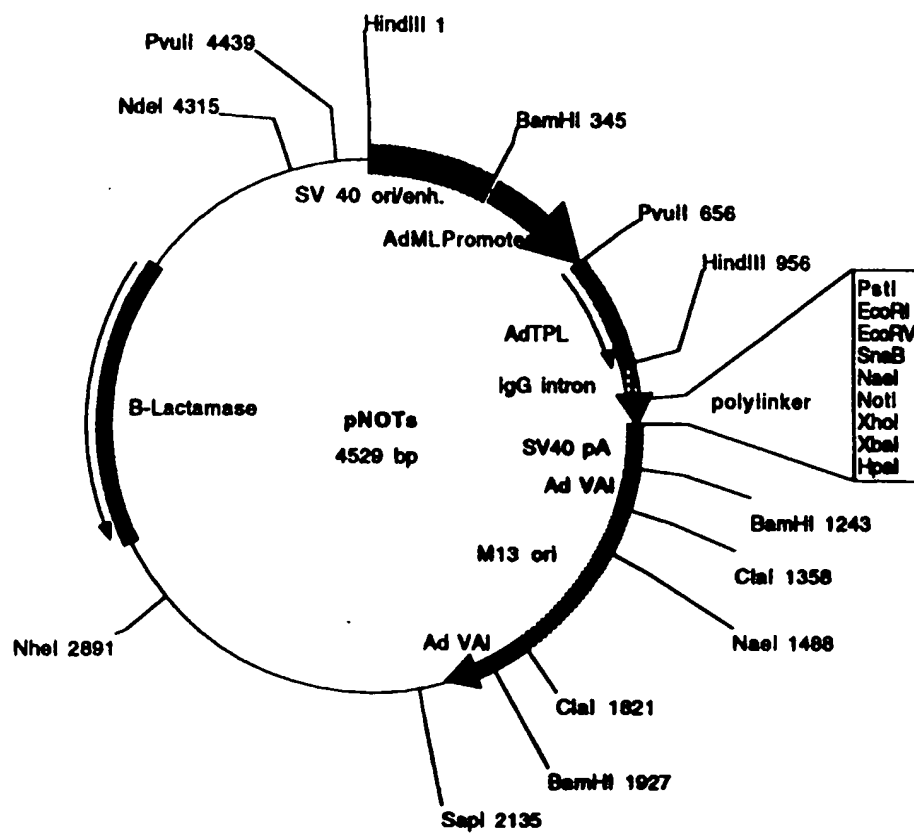


FIGURE 1B



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Treacy, Maurice  
Agostino, Michael J.  
Steininger II, Robert J.  
Genetics Institute, Inc.

"Express Mail" mailing label number. EMS 986844

Date of Deposit: 06 August 1998

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```

&lt;210&gt; 4

&lt;211&gt; 231

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 4

```

Met Gly Ser Gln His Ser Ala Ala Ala Arg Pro Ser Ser Cys Arg Arg
  1              5              10              15

```

```

Lys Gln Glu Asp Asp Arg Asp Gly Leu Leu Ala Glu Arg Glu Gln Glu
              20              25              30

```

```

Glu Ala Ile Ala Gln Phe Pro Tyr Val Glu Phe Thr Gly Arg Asp Ser
      35              40              45

```

```

Ile Thr Cys Leu Thr Cys Gln Gly Thr Gly Tyr Ile Pro Thr Glu Gln
      50              55              60

```

```

Val Asn Glu Leu Val Ala Leu Ile Pro His Ser Asp Gln Arg Leu Arg
      65              70              75              80

```

```

Pro Gln Arg Thr Lys Gln Tyr Val Leu Leu Ser Ile Leu Leu Cys Leu
              85              90              95

```

```

Leu Ala Ser Gly Leu Val Val Phe Phe Leu Phe Pro His Ser Val Leu
      100              105              110

```

```

Val Asp Asp Asp Gly Ile Lys Val Val Lys Val Thr Phe Asn Lys Gln
      115              120              125

```

```

Asp Ser Leu Val Ile Leu Thr Ile Met Ala Thr Leu Lys Ile Arg Asn
      130              135              140

```

```

Ser Asn Phe Tyr Thr Val Ala Val Thr Ser Leu Ser Ser Gln Ile Gln
      145              150              155              160

```

```

Tyr Met Asn Thr Val Val Asn Phe Thr Gly Lys Ala Glu Met Gly Gly
      165              170              175

```

```

Pro Phe Ser Tyr Val Tyr Phe Phe Cys Thr Val Pro Glu Ile Leu Val
      180              185              190

```

```

His Asn Ile Val Ile Phe Met Arg Thr Ser Val Lys Ile Ser Tyr Ile
      195              200              205

```

```

Gly Leu Met Thr Gln Ser Ser Leu Glu Thr His His Tyr Val Asp Cys
      210              215              220

```

```

Gly Gly Asn Ser Thr Ala Ile
      225              230

```



<210> 5  
 <211> 1921  
 <212> DNA  
 <213> Homo sapiens

<400> 5  
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 ccgtctttat tctgtgggct ctgattctcc aatgggaata ccaagggatg gttttccata 180  
 ctggaaccca aaggtaaaga cactcaagga cagacatttt tggcagagca tagatgaaaa 240  
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 tgctcactcc ttgctcagct cagttttctg tgcttggacc ctctgggccc atcctggcca 360  
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 ctcattatca tcaattattat tgctcaccac tgatccccct ctactgggca agtgctgtgc 1860  
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 a 1921

<210> 6  
 <211> 334  
 <212> PRT  
 <213> Homo sapiens

<400> 6  
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 Ser Leu Leu Leu Val Gln Leu Leu Thr Pro Cys Ser Ala Gln Phe Ser  
 20 25 30  
 Val Leu Gly Pro Ser Gly Pro Ile Leu Ala Met Val Gly Glu Asp Ala  
 35 40 45  
 Asp Leu Pro Cys His Leu Phe Pro Thr Met Ser Ala Glu Thr Met Glu  
 50 55 60  
 Leu Lys Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val Tyr Ala  
 65 70 75 80  
 Asp Gly Lys Glu Val Glu Asp Arg Gln Ser Ala Pro Tyr Arg Gly Arg  
 85 90 95

Thr Ser Ile Leu Arg Asp Gly Ile Thr Ala Gly Lys Ala Ala Leu Arg  
 100 105 110  
 Ile His Asn Val Thr Ala Ser Asp Ser Gly Lys Tyr Leu Cys Tyr Phe  
 115 120 125  
 Gln Asp Gly Asp Phe Tyr Glu Lys Ala Leu Val Glu Leu Lys Val Ala  
 130 135 140  
 Ala Leu Gly Ser Asn Leu His Val Glu Val Lys Gly Tyr Glu Asp Gly  
 145 150 155 160  
 Gly Ile His Leu Glu Cys Arg Ser Thr Gly Trp Tyr Pro Gln Pro Gln  
 165 170 175  
 Ile Gln Trp Ser Asn Ala Lys Gly Glu Asn Ile Pro Ala Val Glu Ala  
 180 185 190  
 Pro Val Val Ala Asp Gly Val Gly Leu Tyr Glu Val Ala Ala Ser Val  
 195 200 205  
 Ile Met Lys Gly Gly Ser Gly Glu Gly Val Ser Cys Ile Ile Arg Asn  
 210 215 220  
 Ser Leu Leu Gly Leu Glu Lys Thr Ala Ser Ile Ser Ile Ala Asp Pro  
 225 230 235 240  
 Phe Phe Arg Ser Ala Gln Pro Trp Ile Ala Ala Leu Ala Gly Thr Leu  
 245 250 255  
 Pro Ile Leu Leu Leu Leu Leu Ala Gly Ala Ser Tyr Phe Leu Trp Arg  
 260 265 270  
 Gln Gln Lys Glu Ile Thr Ala Leu Ser Ser Glu Ile Glu Ser Glu Gln  
 275 280 285  
 Glu Met Lys Glu Met Gly Tyr Ala Ala Thr Glu Arg Glu Ile Ser Leu  
 290 295 300  
 Arg Glu Ser Leu Gln Glu Glu Leu Lys Arg Lys Lys Ile Gln Tyr Leu  
 305 310 315 320  
 Thr Arg Gly Glu Glu Ser Ser Ser Asp Thr Asn Lys Ser Ala  
 325 330

&lt;210&gt; 7

&lt;211&gt; 1865

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 7

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 gtcctttag ttaaggctct tgcaaaaagt tgagtgcagg tttaaagcta aaaacacggt 180  
 tttaaacttt cacaaatttt gtaagatgac aatagcattc tgtaacatag acattatggt 240  
 aatagtgatt ttctctccat ccttattttg tccagcgatt tccaagttat aagacgtgaa 300  
 taagactaac cgctcacttc caccagcagc tgacctggtg ggcttttgag ttcaaagagt 360  
 cattttctca tcttacctcc agcactgcag ggccgtgtga ccttgcagag ccttgtttct 420  
 cattgatgaa aggagctcat gcctcatgaa gccactggta agggccatgg agctcacggg 480  
 ccatcaagct tccttcccat cacttggtgg tggaattgac attaccgat gagctcttcc 540  
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 tgcagttttc tccacaggta aatgagatt ttggaaaatt ttcatttggt tgtatttgct 660

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aaaaa 1865

```

&lt;210&gt; 8

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 8

```

Met Asn Val Ser Gln His Ser Leu Ser Phe Ala Pro Lys Lys Arg Ala
  1             5             10             15

```

```

Gly Val Gly Phe Gln Thr Phe Arg Ile Phe Leu Leu Leu Gly Gly
          20             25             30

```

```

Ser Thr Ala Cys Phe Leu Arg Glu Lys Gly Gly Ser Leu Thr Tyr Leu
      35             40             45

```

```

Lys Ala Phe Ser Gln Trp Lys Leu Gly Lys Arg Ile Gln Gly Phe Leu
  50             55             60

```

```

Leu Gln Val Ser Ala Gln Cys Pro Cys His Gln Ala Ala
  65             70             75

```

&lt;210&gt; 9

&lt;211&gt; 2094

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 9

```

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gcttgtctcc ttctaggtct aaaattctga tccttttagta gtttataaat gattattggg 240
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aataattcac aaagctattt gctaattttt gacacttttt tctttgccag taccattaag 540
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aagttacttc tttgtacctg taaagtgaga gtaaaataac atctagtcca taggggtgtt 660
gactagtacc tggcccatgg taactactgt gtcagtgtgg ctgttactac cctttaacat 720
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```

```

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aaaaacaaaa aaacaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 2094

```

&lt;210&gt; 10

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 10

```

Met Ser Ala Arg Thr Gln Phe Ile Cys Leu Ile Gly Phe Ile Lys Leu
  1             5             10             15

```

```

Leu Glu Asn Phe Ser Ile Cys Tyr Phe Phe Pro Leu His Leu Leu Ser
      20             25             30

```

```

Asn Ala Pro Asn Glu Phe Val Thr Gln Ser Gln Leu Phe Pro Ser Leu
      35             40             45

```

```

Ser His Cys Phe Leu Leu Ser Pro Thr His Arg Ile Asn Met Lys Leu
      50             55             60

```

```

Ser Ser Arg Ser Val Met Ile Ser Leu Arg Lys Asn Phe
      65             70             75

```

&lt;210&gt; 11

&lt;211&gt; 2069

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 11

```

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gcgaagtaca gactaatctg aaaaatttga gagaaccact taatattgaa cttaaagaag 300
acattctatc ctatatggaa aaattatggc ttaaaaaaca caggagaact ccacaagagc 360
aactttttta aatgctacca gatacgttcc cacatccaca tgaaaccact ggtgatgcac 420
agtgttctca aaatgaaaac gatgaagata gtgatggtga ggagaccaa gtacaacaca 480
cagctctttt attgccagta gaaacattaa acatagagag acctgaacca tctctaaaga 540
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acaaagttaa attagctgat gcagacagtc aacgaagttg tgcttttcat gattgtcaga 660
agaatagctt tccatatgaa aatggcatcc atcaacatca tgttttcgat aagggaaga 720

```

```

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cagaccatag cttaagtga tatgctgata atgcaattgt cttgggtgtt ctgcagggtg 1320
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tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2069

```

&lt;210&gt; 12

&lt;211&gt; 605

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 12

Met Lys Arg Ala Gln Arg Thr Lys Pro Arg Lys Ser Leu Leu Cys Glu  
1 5 10 15

Gly Ser Phe Asp Glu Glu Ala Ser Ala Gln Ser Phe Gln Glu Val Leu  
20 25 30

Ser Gln Trp Arg Thr Gly Asn His Asp Asp Asn Lys Lys Gln Asn Leu  
35 40 45

His Ala Ala Val Lys Asp Ser Leu Glu Glu Cys Glu Val Gln Thr Asn  
50 55 60

Leu Lys Ile Trp Arg Glu Pro Leu Asn Ile Glu Leu Lys Glu Asp Ile  
65 70 75 80

Leu Ser Tyr Met Glu Lys Leu Trp Leu Lys Lys His Arg Arg Thr Pro  
85 90 95

Gln Glu Gln Leu Phe Lys Met Leu Pro Asp Thr Phe Pro His Pro His  
100 105 110

Glu Thr Thr Gly Asp Ala Gln Cys Ser Gln Asn Glu Asn Asp Glu Asp  
115 120 125

Ser Asp Gly Glu Glu Thr Lys Val Gln His Thr Ala Leu Leu Leu Pro  
130 135 140

Val Glu Thr Leu Asn Ile Glu Arg Pro Glu Pro Ser Leu Lys Ile Val  
145 150 155 160

Glu Leu Asp Asp Thr Tyr Glu Glu Glu Phe Glu Glu Ala Glu Asn Ile  
165 170 175

Val Pro Tyr Lys Val Lys Leu Ala Asp Ala Asp Ser Gln Arg Ser Cys  
 180 185 190  
 Ala Phe His Asp Cys Gln Lys Asn Ser Phe Pro Tyr Glu Asn Gly Ile  
 195 200 205  
 His Gln His His Val Phe Asp Lys Gly Lys Arg Asp Phe Leu Asn Leu  
 210 215 220  
 Cys Leu Arg Asn Ser Tyr Thr Tyr Tyr Lys Asp Asn Ser Lys Ala Glu  
 225 230 235 240  
 Thr Ser Asn Thr Asp Phe Asp Asn Ile Val Asp Pro Asp Val Tyr Ser  
 245 250 255  
 Ser Asp Ile Glu Lys Ile Glu Glu Ser Thr Ser Phe Glu Arg Asn Leu  
 260 265 270  
 Lys Glu Lys Asn Ile Gly Leu Glu Ser Asn Gln Lys Ser Asp Asp Ser  
 275 280 285  
 Cys Val Ser Leu Glu Ser Lys Asp Thr Leu Leu Gly Arg Asp Leu Glu  
 290 295 300  
 Lys Ala Pro Ile Glu Glu Lys Leu Ser Gln Asp Ile Lys Glu Ser Leu  
 305 310 315 320  
 Glu Leu Ser Asn Leu Tyr Lys Arg Pro Ser Phe Glu Glu Ser Lys Thr  
 325 330 335  
 Thr Lys Ser Ser Leu Leu Leu Gln Glu Ile Ala Cys Arg Ser Lys Pro  
 340 345 350  
 Ile Thr Lys Gln Tyr Gln Gly Leu Glu Arg Phe Phe Ile Phe Asp Thr  
 355 360 365  
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 370 375 380  
 Ser Ser Thr Arg Ile Thr Leu Ala Glu Asp Arg Glu Trp Ile Pro Asp  
 385 390 395 400  
 His Ser Leu Ser Glu Tyr Ala Asp Asn Ala Ile Val Leu Gly Val Leu  
 405 410 415  
 Gln Gly Ala Gln Ser Pro Ser Ser Ser Arg Lys Gln Gln Lys Met Gly  
 420 425 430  
 Gln Lys Ser Gln Arg Pro Ser Thr Ala Asn Phe Pro Leu Ser Asn Ser  
 435 440 445  
 Val Lys Glu Ser Ser Ser Cys Leu Ser Ser Ser His Pro Arg Ser Arg  
 450 455 460  
 Ser Ala Ala Ala Gln Ser Ser Ser Arg Ala Ala Ser Glu Ile Ser Glu  
 465 470 475 480  
 Ile Glu Tyr Ile Asp Ile Thr Asp Gln Asn Glu Leu Ser Leu Asp Asp  
 485 490 495  
 Thr Thr Asp Gln His Thr Leu Asp Asn Leu Glu Lys Glu Leu Gln Val  
 500 505 510

Leu Arg Ser Leu Ala Asp Thr Ser Glu Lys Leu Tyr Ser Leu Thr Ser  
 515 520 525  
 Glu Glu Phe Pro Asp Phe Ser Ser Gln Ser Leu Asn Ile Ser Gln Ile  
 530 535 540  
 Ser Thr Asp Phe Leu Lys Thr Ser His Val Arg Gly Pro Cys Gly Val  
 545 550 555 560  
 Glu Glu Leu Ser Cys Ser Gly Arg Asp Thr Lys Ile Gln Ser Leu Leu  
 565 570 575  
 Ser Leu Ser Glu Ser Ser Thr Asp Glu Glu Glu Asp Phe Leu Asn  
 580 585 590  
 Lys Gln His Val Ile Thr Leu Pro Trp Ser Lys Ser Thr  
 595 600 605

&lt;210&gt; 13

&lt;211&gt; 4337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

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&lt;211&gt; 903

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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Asn Gly Leu Asp Glu Ser Phe Cys Gly Arg Thr Leu Arg Asn Arg Ser  
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Ile Ala His Pro Glu Glu Ile Ser Ser Asn Ser Gln Val Arg Ser Arg  
35 40 45

Ser Pro Lys Lys Arg Pro Glu Pro Val Pro Ile Gln Lys Gly Asn Asn  
50 55 60

Asn Gly Arg Thr Thr Asp Leu Lys Gln Gln Ser Thr Arg Glu Ser Trp  
65 70 75 80

Val Ser Pro Arg Lys Arg Gly Leu Ser Ser Ser Glu Lys Asp Asn Ile  
85 90 95

Glu Arg Gln Ala Ile Glu Asn Cys Glu Arg Arg Gln Thr Glu Pro Val  
100 105 110



Ser Pro Val Leu Lys Arg Ile Lys Arg Cys Leu Arg Ser Glu Ala Pro  
 115 120 125  
 Asn Ser Ser Glu Glu Asp Ser Pro Ile Lys Ser Asp Lys Glu Ser Val  
 130 135 140  
 Glu Gln Arg Ser Thr Val Val Asp Asn Asp Ala Asp Phe Gln Gly Thr  
 145 150 155 160  
 Lys Arg Ala Cys Arg Cys Leu Ile Leu Asp Asp Cys Glu Lys Arg Glu  
 165 170 175  
 Ile Lys Lys Val Asn Val Ser Glu Glu Gly Pro Leu Asn Ser Ala Val  
 180 185 190  
 Val Glu Glu Ile Thr Gly Tyr Leu Ala Val Asn Gly Val Asp Asp Ser  
 195 200 205  
 Asp Ser Ala Val Ile Asn Cys Asp Asp Cys Gln Pro Asp Gly Asn Thr  
 210 215 220  
 Lys Gln Asn Ser Ile Gly Ser Tyr Val Leu Gln Glu Lys Ser Val Ala  
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 Glu Asn Gly Asp Thr Asp Thr Gln Thr Ser Met Phe Leu Asp Ser Arg  
 245 250 255  
 Lys Glu Asp Ser Tyr Ile Asp His Lys Val Pro Cys Thr Asp Ser Gln  
 260 265 270  
 Val Gln Val Lys Leu Glu Asp His Lys Ile Val Thr Ala Cys Leu Pro  
 275 280 285  
 Val Glu His Val Asn Gln Leu Thr Thr Glu Pro Ala Thr Gly Pro Phe  
 290 295 300  
 Ser Glu Thr Gln Ser Ser Leu Arg Asp Ser Glu Glu Glu Val Asp Val  
 305 310 315 320  
 Val Gly Asp Ser Ser Ala Ser Lys Glu Gln Cys Lys Glu Asn Thr Asn  
 325 330 335  
 Asn Glu Leu Asp Thr Ser Leu Glu Ser Met Pro Ala Ser Gly Glu Pro  
 340 345 350  
 Glu Pro Ser Pro Val Leu Asp Cys Val Ser Ala Gln Met Met Ser Leu  
 355 360 365  
 Ser Glu Pro Gln Glu His Arg Tyr Thr Leu Arg Thr Ser Pro Arg Arg  
 370 375 380  
 Ala Ala Pro Thr Arg Gly Ser Pro Thr Lys Asn Ser Ser Pro Tyr Arg  
 385 390 395 400  
 Glu Asn Gly Gln Phe Glu Glu Asn Asn Leu Ser Pro Asn Glu Thr Asn  
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 Ala Thr Val Ser Asp Asn Val Ser Gln Ser Pro Thr Asn Pro Gly Glu  
 420 425 430  
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Ser Glu Gly Val Ser Lys Pro Pro Ser Glu Ala Arg Leu Asn Ile Gly  
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 His Leu Pro Ser Ala Lys Glu Ser Ala Ser Gln His Ile Thr Glu Glu  
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 Glu Asp Asp Asp Pro Asp Val Tyr Tyr Phe Glu Ser Asp His Val Ala  
 485 490 495  
 Leu Lys His Asn Lys Asp Tyr Gln Arg Leu Leu Gln Thr Ile Ala Val  
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 Leu Glu Ala Gln Arg Ser Gln Ala Val Gln Asp Leu Glu Ser Leu Gly  
 515 520 525  
 Arg His Gln Arg Glu Ala Leu Lys Asn Pro Ile Gly Phe Val Glu Lys  
 530 535 540  
 Leu Gln Lys Lys Ala Asp Ile Gly Leu Pro Tyr Pro Gln Arg Val Val  
 545 550 555 560  
 Gln Leu Pro Glu Ile Val Trp Asp Gln Tyr Thr His Ser Leu Gly Asn  
 565 570 575  
 Phe Glu Arg Glu Phe Lys Asn Arg Lys Arg His Thr Arg Arg Val Lys  
 580 585 590  
 Leu Val Phe Asp Lys Val Gly Leu Pro Ala Arg Pro Lys Ser Pro Leu  
 595 600 605  
 Asp Pro Lys Lys Asp Gly Glu Ser Leu Ser Tyr Ser Met Leu Pro Leu  
 610 615 620  
 Ser Asp Gly Pro Glu Gly Ser Ser Ser Arg Pro Gln Met Ile Arg Gly  
 625 630 635 640  
 Arg Leu Cys Asp Asp Thr Lys Pro Glu Thr Phe Asn Gln Leu Trp Thr  
 645 650 655  
 Val Glu Glu Gln Lys Lys Leu Glu Gln Leu Leu Ile Lys Tyr Pro Pro  
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 Glu Glu Val Glu Ser Arg Arg Trp Gln Lys Ile Ala Asp Glu Leu Gly  
 675 680 685  
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 Tyr Ile Tyr Ser Lys Lys Ser Ser Thr Ser Arg Arg Gln His Pro Leu  
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 Asn Lys His Leu Phe Lys Pro Ser Thr Phe Met Thr Ser His Glu Pro  
 740 745 750  
 Pro Val Tyr Met Asp Glu Asp Asp Arg Ser Cys Phe His Ser His  
 755 760 765  
 Met Asn Thr Ala Val Glu Asp Ala Ser Asp Asp Glu Ser Ile Pro Ile  
 770 775 780

Met Tyr Arg Asn Leu Pro Glu Tyr Lys Glu Leu Leu Gln Phe Lys Lys  
 785 790 795 800

Leu Lys Lys Gln Lys Leu Gln Gln Met Gln Ala Glu Ser Gly Phe Val  
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Gln His Val Gly Phe Lys Cys Asp Asn Cys Gly Ile Glu Pro Ile Gln  
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Gly Val Arg Trp His Cys Gln Asp Cys Pro Pro Glu Met Ser Leu Asp  
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Phe Cys Asp Ser Cys Ser Asp Cys Leu His Glu Thr Asp Ile His Lys  
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Glu Asp His Gln Leu Glu Pro Ile Tyr Arg Ser Glu Thr Phe Leu Asp  
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Arg Asp Tyr Cys Val Ser Gln Gly Thr Ser Tyr Asn Tyr Leu Asp Pro  
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Asn Tyr Phe Pro Ala Asn Arg  
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 aacaccccaga ccctgcctcc ctcaggcacc agatccagtg tcctagtga acgctggatc 240  
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 <212> PRT  
 <213> Homo sapiens

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 35 40 45  
 Ser Thr Pro Cys Ile Pro Thr Leu His Ser Ile Phe His Pro Pro Pro  
 50 55 60  
 Thr Ser Arg Arg Ile Val Pro Arg Ala Val Phe Leu Gln Gly Val Arg  
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 85 90 95

Asp Thr

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 <212> DNA  
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<210> 18  
 <211> 185  
 <212> PRT  
 <213> Homo sapiens

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 Ala Gly Ser Gly Gln Gln Ser Val Ser Val Asn Asn Glu His Asn Val  
 35 40 45  
 Ala Asn Val Asp Asn Asn Asn Gly Trp Asp Ser Trp Asn Ser Ile Trp  
 50 55 60  
 Asp Tyr Gly Asn Gly Phe Ala Ala Thr Arg Leu Phe Gln Lys Lys Thr  
 65 70 75 80  
 Cys Ile Val His Lys Met Asn Lys Glu Val Met Pro Ser Ile Gln Ser  
 85 90 95

Leu Asp Ala Leu Val Lys Glu Lys Lys Leu Gln Gly Lys Gly Pro Gly  
 100 105 110  
 Gly Pro Pro Pro Lys Gly Leu Met Tyr Ser Val Asn Pro Asn Lys Val  
 115 120 125  
 Asp Asp Leu Ser Lys Phe Gly Lys Asn Ile Ala Asn Met Cys Arg Gly  
 130 135 140  
 Ile Pro Thr Tyr Met Ala Glu Glu Met Gln Glu Ala Ser Leu Phe Phe  
 145 150 155 160  
 Tyr Ser Gly Thr Cys Tyr Thr Thr Ser Val Leu Trp Ile Val Asp Ile  
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 Ser Phe Cys Gly Asp Thr Val Glu Asn  
 180 185

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 <212> DNA  
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<210> 20  
 <211> 502  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 20

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Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg  
 35 40 45

Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser  
 50 55 60

Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu  
 65 70 75 80

Gln Phe Thr Arg Val Gly Val Gln Val Leu Asp Arg Lys Asp Gly Ser  
 85 90 95

Phe Ile Val Arg Tyr Arg Met Tyr Ala Ser Tyr Lys Asn Leu Lys Val  
 100 105 110

Glu Ile Lys Phe Gln Gly Gln His Val Ala Lys Ser Pro Tyr Ile Leu  
 115 120 125

Lys Gly Pro Val Tyr His Glu Asn Cys Asp Cys Pro Leu Gln Asp Ser  
 130 135 140

Ala Ala Trp Leu Arg Glu Met Asn Cys Pro Glu Thr Ile Ala Gln Ile  
 145 150 155 160

Gln Arg Asp Leu Ala His Phe Pro Ala Val Asp Pro Glu Lys Ile Ala  
 165 170 175

Val Glu Ile Pro Lys Arg Phe Gly Gln Arg Gln Ser Leu Cys His Tyr  
 180 185 190

Thr Leu Lys Asp Asn Lys Val Tyr Ile Lys Thr His Gly Glu His Val  
 195 200 205

Gly Phe Arg Ile Phe Met Asp Ala Ile Leu Leu Ser Leu Thr Arg Lys  
 210 215 220

Val Lys Met Pro Asp Val Glu Leu Phe Val Asn Leu Gly Asp Trp Pro  
 225 230 235 240

Leu Glu Lys Lys Lys Ser Asn Ser Asn Ile His Pro Ile Phe Ser Trp  
 245 250 255

Cys Gly Ser Thr Asp Ser Lys Asp Ile Val Met Pro Thr Tyr Asp Leu  
 260 265 270

Thr Asp Ser Val Leu Glu Thr Met Gly Arg Val Ser Leu Asp Met Met  
 275 280 285

Ser Val Gln Ala Asn Thr Gly Pro Pro Trp Glu Ser Lys Asn Ser Thr  
 290 295 300

Ala Val Trp Arg Gly Arg Asp Ser Arg Lys Glu Arg Leu Glu Leu Val  
 305 310 315 320

Lys Leu Ser Arg Lys His Pro Glu Leu Ile Asp Ala Ala Phe Thr Asn  
 325 330 335  
 Phe Phe Phe Phe Lys Gln Asp Glu Asn Leu Tyr Gly Pro Ile Val Lys  
 340 345 350  
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 355 360 365  
 Asp Gly Thr Val Ala Ala Tyr Arg Leu Pro Tyr Leu Leu Val Gly Asp  
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 Ser Val Val Leu Lys Gln Asp Ser Ile Tyr Tyr Glu His Phe Tyr Asn  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/16318

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : 435/69.1, 252.3, 320.1; 536/23.1, 23.5, 24.31; 530/350; 514/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1, 252.3, 320.1; 536/23.1, 23.5, 24.31; 530/350; 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog and APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,536,637 A (JACOBS) 16 July 1996, col. 1-6.	1-11
Y	Database GenBank, Accession No. X95828G. GIZATULLIN et al. "H. sapiens DNA NotI jumping clone J32A032D.", 1996.	1-11
Y	Database GenBank, Accession No. AA143257. HILLIER et al. "zo36b06.r1 Stratagene endothelial cell 937223 Homo sapiens cDNA clone 588947 5'". 1996.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 SEPTEMBER 1998

Date of mailing of the international search report

14 OCT 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/16318

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/16318

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): C12N 15/00, 15/11, 1/21, 15/63; C07H 21/02, 21/04; C07K 14/00; A61K 38/00

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-11, drawn to polynucleotides and proteins encoding or related to SEQ ID NO:1 and 2.

Group II, claim(s) 12-14, drawn to polynucleotides and proteins encoding or related to SEQ ID NO:3 and 4.

Group III, claim(s) 15-17, drawn to polynucleotides and proteins encoding or related to SEQ ID NO:5 and 6.

Group IV, claim(s) 18-20 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:7 and 8.

Group V, claim(s) , 21-23 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:9 and 10.

Group VI, claim(s) , 24-26 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:11 and 12.

Group VII, claim(s), 27-29 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:13 and 14.

Group VIII, claim(s) , 30-32 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:15 and 16.

Group IX, claim(s) , 33-35 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:17 and 18.

Group X, claim(s) , 36-38 drawn to polynucleotides and proteins encoding or related to SEQ ID NO:19 and 20.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the polynucleotide and polypeptide sequences within each group are related to each other by virtue of the fact that the DNA encodes the protein. The polynucleotide and polypeptide sequences of each of the separate groups are not so related, therefore, the inventions of each of the separate groups lack the same or corresponding special technical features.